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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/849,967	05/08/2001	Stuart A. Newman	51230-00601	1338

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EXAMINER
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YU, MISOOK

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/849,967

**Applicant(s)**

NEWMAN ET AL.

**Examiner**

MISOOK YU, Ph.D.

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-15, 21, 29-30, 55-64 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-15, 21, 29, 30, 55-64 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicant's amendment filed on 11/04/2004 is acknowledged. Claims 1, 21, 29, 30, 57, 59, 61, and 63 are amended. Claims 1-15, 21, 29-30, and 55-64 are pending and under consideration.

This Office action contains new grounds of rejection.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***Claim Rejections - 35 USC § 112***

The rejection of Claims 21, and 30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in view of the amendment.

The rejection of claims 1-15, 21, 29, 30, 55-64 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in view of deleting "in trans".

Claims 1-15, 21, 29, 30, and 55-64 **remain rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated before in the previous Office action mailed on 05/04/2004, the nature of invention is interpreted as broadly drawn to method of modifying hnRNP A protein by introducing (using various art-known method of introducing nucleic acids into a cell) into a cell a plurality of RNA polynucleotide sequences with sufficient homology to a portion of FGFR2 exon 8 capable of binding an hnRNP A protein, or introducing into a cell a plurality of polynucleotide sequence comprising any ESS (exonic splicing silencer), ESE (exonic splicing enhancer), ISS (intronic splicing silencer), or ISE (intronic splicing enhancer) into any cell.

Applicant argues that the limitation "in trans" has been deleted, and hnRNP A1 proteins including their RNA binding sites are highly conserved throughout many species as described in paragraph 318 of the specification, in particular the homology between the human and chicken hnRNP A1 and their RNA binding sites are shown in Fig. 1b, and 2. Based upon the highly conserved nature of the hnRNP A1 proteins and their RNA binding sites across species, it naturally follows that the RNA sequences that are capable of binding to these sites must also be sufficiently homologous across species. These arguments have been fully considered but found unpersuasive.

As stated before at page 9-11~~§~~ in the previous Office action mailed on 5/4/2004, Maniatis and Tasic (2002, Nature, vol. 236, pages 236-243) at page 236, right column, 4<sup>th</sup> line teaches "5' and 3' splice sites are poorly conserved". This implies that a sequence prediction for splicing sites based on a known sequence is a difficult task. The specification does not teach how to make the RNA polynucleotide sequences comprising sequences with sufficient homology to at least a portion of FGFR2 exon 8

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capable of binding to the hnRNP A protein. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

The specification discloses: at Fig.1b, chicken hnRNP A1 amino acids sequences; three different isoforms of human hnRNP proteins i.e. hnRNP A1, A1<sup>B</sup>, and A2 have been discovered so far; Examples 1 at page 59, chicken cells electroporated with 138 base sense transcript from the chicken *fgfr2lllc* mRNA containing the ESS corresponding to exon 8 showed a phenotype in cartilage formation that is different from the control cells electroporated with a different sense transcript that does not contain ESS. The specification does not teach whether introduction of the chicken *fgfr2lllc* mRNA containing the ESS corresponding to exon 8 (see Example 1 at page 59 of the specification) into HIV infected human T cells would result in modifying hnRNP A protein of said T cells. The specification does not teach what kind of phenotype one has to look for in order to determine whether the introduced sequence modified hnRNP protein or not. But it is not clear whether introducing the HIV tat exon containing ESS into an avian cell (see construction of instant claim 1 vs. 9) would result in the purpose stated in the preamble of the claims.

Maniatis and Tasic (2002, Nature, vol. 236, pages 236-243) teach that pre-mRNA splicing is carried out by multicomponent ribonucleoprotein complexes, called spliceosomes that recognize 5' and 3' splice sites, which are located at exon-intron boundaries. There are multiple other splicing factors (hnRNP A is one of them) that bind to ESEs (see Fig. 1). Multiple proteins for example, both hnRNP A1 and SF2/ASF

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can bind to the same ESE sites depending on the in vivo situations (note page 238, left column, 1<sup>st</sup> paragraph). For example, if ESS in an exon of HIV tat pre-mRNA, the one shown Fig. 1 of Caputi et al., (1999, The EMBO Journal, vol. 18, pages 4060-67) is introduced into a cell, either hnRNP A1 protein, or SF2/ASF could bind to the introduced sequence. Maniatis and Tasic teach that SF2/ASF has a higher affinity for the sequence i.e. HIV tat pre-mRNA than hnRNP A1 protein. Thus, the introduced sequence could easily compete in trans with at least one endogenous RNA sequence for interacting with the SF2/ASF protein, instead of the intended hnRNP A protein or hnRNP A protein. The specification does not teach how to chase away the SF2/ASF protein inside cell, while making the introduced sequence to interact with hnRNP A1 protein. The specification fails to teach that the phenotype seen by introducing the polynucleotide containing ESS (i.e. chicken cartilage formation in Example 1) is whether competition of the introduced sequence in trans occurred with at least one endogenous RNA sequence for interacting with SF2/ASF or hnRNP A1 protein. The specification does not teach the polynucleotide sequence that only hnRNP A, or A1 protein binds to. However, Maniatis and Tasic teach that depending on the in vivo conditions such as developmental stages for example, during embryogenesis, the same ESS, ESE, ISS, and/or ISE are bound by different splicing proteins. This results in producing different isoforms from a single pre-mRNA. In other words, the same polynucleotides are used over and over by different splicing proteins in concerted manner (i.e. one binding to one ESE lead to second ESE binding in cooperative way) to meet the need of cells or virus at the moment. This concerted effort inside cells has not been teased out yet and it is

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difficult to modify only one splicing factor, without affecting the other numerous splicing factors.

In summary, the claims as currently construed say that introduction of polynucleotide capable of binding RNP A protein, or introduction of polynucleotide comprising ESS, ESE, or ISS, or ISE into any cell would result in modifying hnRNP A protein but the art teaches that it is difficult to predict what is going to happen to the introduced once entered into a cell because numerous other splicing factors also compete for binding of same sequences. The specification does not teach how to make ISS, ISE, ESS, ESE, or polynucleotide sequences capable of binding any hnRNP A protein. Is there a universal ISS, ISE, ESS, and/or ESE for all hnRNP A proteins? The art mostly teaches ISS, ISE, ESS, ESE, or polynucleotide sequences capable of binding **human** hnRNP A1 protein. The instant claims say introduction of ISS, ISE, ESS, ESE, or polynucleotide sequences capable of binding hnRNP A into non-human cells and it is not clear ISS, ISE, ESS, ESE, or polynucleotide sequences capable of binding human hnRNP A1 protein would work in dog cells that express dog hnRNP A1 protein. The specification fails to teach the issues raised above.

Considering the unpredictable state of art and low skill in the art, limited guidance, no examples in the specification how to use the instantly claimed invention, broad breath of the claims, it is concluded that undue experimentation is required to practice the invention.

***Claim Rejections - 35 USC § 102***

The rejection of Claims 1, 3-6, 15, 29, and 30, 55-60 under 35 U.S.C. 102(b) as being anticipated by Blanchette et al (Apr 1, 1999, The EMBO Journal, vol. 18, pages

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1939-1952) as evidenced by Sambrook et al (1989, Molecular Cloning, A Laboratory Manual, 2<sup>nd</sup> Edition, pages 16.30-16.33) for claim 5 is **withdrawn** because the amended claims are no longer anticipated by Blanchette et al.

Claims 1, 3, 14, 15, 21, 29, 30, 55, 56, 57, 58, 61-64 **remain rejected** under 35 U.S.C. 102(b) as being anticipated by Purcell and Martin (J. Virol., 1993, vol. 67, pages 6365-78) as evidenced by Damgaard et al., (2002, RNA, vol. 8, pages 1401-1415) and by Section 2. Virology (total 5 pages) of Medical Microbiology (S. Baron, ed) downloaded from [url>>cbi.nlm.nih.gov/books](http://cbi.nlm.nih.gov/books) on 4/20/2004.

Claims 1, 3, 14, 15, 21, 29, 30, 55, 56, 57, 58, 61-64 are interpreted as drawn to method with only one manipulative active step i.e. introducing into a cell a plurality of RNA polynucleotide sequences with sufficient homology to a portion of FGFR2 exon 8, wherein the introduced sequences has a sufficient homology capable of binding an hnRNP A protein (claims 1, 3, 14, 15, 21) by applying said polynucleotide sequence to said cell (claim 3), or a plurality of polynucleotide sequences capable of binding hnRNP A1 (claims 29, and 30), a plurality of polynucleotide sequences comprising an intronic splicing silencer (ISS) (claims 57, and 58), a plurality of polynucleotide sequences comprising exonic splicing silencer (ESS), (claims 61, and 62), a plurality of polynucleotide sequences comprising exonic splicing enhancer (ESE) (claims 63 and 64), wherein the introduced polynucleotide sequences compete in trans with at least one endogenous RNA sequence for interacting with the hnRNP A protein or hnRNP A1 protein.

Applicant argues that the product used in the amended claims is different from the HIV genome of Purcell and Marin used in the study of infecting HIV-1 virus to lymphocytes or human T-cell lines by contacting the cell lines with HIV-1 virus.

This argument has been fully considered but found unpersuasive because the amended claims 1, 3, 14, 15, 21, 29, 30, 55, 56, 57, 58, 61-64 as currently construed still read on the procedure of infecting HIV-1 virus to lymphocytes or human T-cell lines by contacting said cell lines with HIV-1 virus disclosed in lines 4-5 of abstract, and page 6366, right column, under the heading "Cell culture, transfections, and infections", page 6374 under the heading "Infectivity of splicing mutants of HIV-1" of Purcell and Martin (cited above) because HIV-1 RNA inherently has ESS (as evidenced by Damgaard et al., note abstract, page 1403, Table 1) that hnRNP A1 (species of hnRNP A) binds to. Since the amended base claims are construed with the open transitional phrases "comprising", the HIV-1 genome, which comprises ESS, ISS, and ESE is "RNA polynucleotide sequences comprising sequences with sufficient homology to at least a portion of FGFR2 exon 8 capable of binding to the hnRNP A protein", "RNA polynucleotide sequence comprising at least one intronic silencer", "RNA polynucleotide sequence comprising at least one exonic silencer", or RNA polynucleotide sequence comprising at least one exonic silencer".

***Claim Rejections - 35 USC § 103, Withdrawn***

The rejection of Claim under 35 U.S.C. 103(a) as being unpatentable over Blanchette et al (Apr 1, 1999, The EMBO Journal, vol. 18, pages 1939-1952) as applied

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to claims 1, 3-6, 15, 29, and 30, 55-60 above, and further in view of Sambrook et al (1989, Molecular Cloning, A Laboratory Manual, 2<sup>nd</sup> Edition, pages 16.30-16.33) is withdrawn because Blanchette et al., is no longer ~~an~~ art.

***The Following Are New Grounds of Rejection***

***Claim Rejections - 35 USC § 112***

Claims 1-15, 21, 29, 30, 55, and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has two parts.

First, the claims are rejected for failing to provide written description for the claimed genus of RNAs being used in the claimed method. The amended base claims 1, and 29 are drawn to method of using a RNA sequence "sufficient homology to at least a portion of FGFR2 exon 8 capable of binding to the hnRNP A protein"

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics

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of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In this case, the only factor present in the claim is a partial structure in the form of sufficient homology to at least a portion of FGFR2 exon 8 capable of binding to the hnRNP A protein. If at least a portion of FGFR2 exon 8 is capable of binding to the hnRNP protein, but the claims do not describe any functional characteristics of the genus encompassed by the sequence with "sufficient homology" to the at least a portion of FGFR2 exon 8 capable of binding to the hnRNP A protein. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Second, the claims are rejected because the amended claims contain new matter not supported by the specification as originally filed. The Office is unable to locate the support for the new limitation "sequences with sufficient homology" at least a portion of FGFR2 exon 8 capable of binding to the hnRNP A protein". The specification at pages 58, and 59 (Example 1) discloses that FGFR2 exon 8 contains ESS capable of binding to a hnRNP A protein. However, the specification as originally filed does not discloses that sequences with sufficient homology" at least a portion of FGFR2 exon 8 capable of binding to the hnRNP A protein are intronic splicing silencers, intronic splicing enhancers, or exonic splicing enhancers as specified in instant claim 55, which depends on the amended claim 1. The specification as originally filed does not disclose

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that "sequences with sufficient homology" at least a portion of FGFR2 exon 8 are intronic splicing silencers, intronic splicing enhancers, or exonic splicing enhancers. Rather, the specification as originally filed discloses that at least a portion of FGFR2 exon 8 contains exonic splicing silencer.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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PRIMARY EXAMINER

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